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Combination Antibody Therapy With Epratuzumab and Rituximab in Relapsed or Refractory Non-Hodgkin's Lymphoma

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A B S T R A C T

Purpose
To explore the safety and therapeutic activity of combination anti–B-cell monoclonal antibody therapy in non-Hodgkin's lymphoma (NHL).

Patients and Methods
Twenty-three patients with recurrent B-cell lymphoma received anti-CD22 epratuzumab 360 mg/m^2 and anti-CD20 rituximab 375 mg/m^2 monoclonal antibodies weekly for four doses each. Sixteen patients had indolent histologies (15 with follicular lymphoma) and seven had aggressive NHL (all diffuse large B-cell lymphoma [DLBCL]). Indolent patients had received a median of one (range, one to six) prior treatment, with 31% refractory to their last therapy and 81% with high-risk Follicular Lymphoma International Prognostic Index scores. Patients with DLBCL had a median of three (range, one to eight) prior regimens (14% resistant to last treatment) and 71% had high intermediate–risk or high-risk International Prognostic Index scores. All patients were rituximab naïve.

Results
Treatment was well tolerated, with toxicities principally infusion-related and predominantly grade 1 or 2. Ten (67%) patients with follicular NHL achieved an objective response (OR), including nine of 15 (60%) with complete responses (CRs and unconfirmed CRs). Four of six assessable patients (67%) with DLBCL achieved an OR, including three (50%) CRs. Median time to progression for all indolent NHL patients was 17.8 months.

Conclusion
The full-dose combination of epratuzumab with rituximab was well tolerated and had significant clinical activity in NHL, suggesting that this combination should be tested in comparison with single-agent treatment.

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoid neoplasms, with diverse molecular characteristics, biology, clinical presentation, response to treatment, and survival.[1-4] Despite the high response rate of indolent NHL to initial therapy, subsequent therapeutic interventions generally are progressively less effective in controlling disease, and cure is not usually expected.[5,6] Diffuse large-cell NHL can be cured with first-line combination chemotherapy, but nearly 50% of patients will have progressive disease after primary therapy, requiring subsequent treatment that is associated with substantially lower cure rates.[5-9]

Rituximab (Rituxan; Genentech Inc, South San Francisco, CA; and Biogen Idec Pharmaceuticals, San Diego, CA), the first monoclonal antibody (MAb) approved for

the treatment of CD20-positive B-cell NHL in 1997, is a human-mouse chimeric immunoglobulin G1 (IgG1) MAb.[10] It targets the CD20 antigen present on B cells and produces rapid and severe B-cell depletion. Although rituximab is useful as a monotherapy and in combination with chemotherapy for various forms of NHL, virtually all patients experience disease relapse after single-agent treatment.[10] Given that another B-cell antigen, CD22, is also abundantly expressed in a similar pattern and frequency as CD20 in B-cell NHL,[11] we examined a humanized anti-CD22 MAb, epratuzumab, in dose-escalation trials of NHL patients with indolent and aggressive disease.[12,13]

The encouraging safety and efficacy results obtained as a monotherapy given once weekly during 4 weeks stimulated our interest in examining whether administration of full doses of epratuzumab combined with rituximab would be well tolerated and could perhaps enhance responses compared with the known experience with either antibody alone. This logical next step in the development of immunotherapy of NHL explores the concept that agents targeting two different antigen sites on cancer cells, which may at least in part have different mechanisms of action, might have additive or synergistic antilymphoma effects or could potentially overcome single-agent resistance. In this phase II study, we report the first results in patients with relapsed/refractory indolent and aggressive NHL receiving a combination of two anti–B-cell antibodies, epratuzumab and rituximab.

PATIENTS AND METHODS

Study Design

This was a phase II single-center trial evaluating four intravenous infusions of the chimeric anti-CD20 MAb, rituximab, combined with epratuzumab, a humanized anti-CD22 antibody, in patients with relapsed or refractory indolent or aggressive NHL. The objectives were to evaluate the tolerability, safety, dose-limiting toxicities, immunogenicity, and clinical activity of the combined antibody immunotherapy. Initially, seven patients received the first dose of epratuzumab on the first day, followed by rituximab 2 days later. After the safety of this combination was confirmed, subsequent patients received epratuzumab followed within 1 hour by rituximab, infused during 4 to 6 hours on the same day. Infusions of both agents were administered weekly for 4 consecutive weeks, with assessments for response and toxicity performed 4 weeks after the last infusion. The patients were re-evaluated every 3 to 4 months for the first 2 years, and every 6 months thereafter until disease progression.

Antibodies

Epratuzumab (humanized IgG1 [κ], anti-CD22 monoclonal antibody [hLL2]) was produced and subjected to quality control at Immunomedics Inc (Morris Plains, NJ), and was administered at dose of 360 mg/m²/wk. Rituximab (chimeric IgG1 [κ], anti-CD20 monoclonal antibody) was administered at a dose of 375 mg/m²/wk for 4 consecutive weeks; each infusion occurred after the

administration of epratuzumab, except in the first cohort of patients (as described above).

Study Population

Patients at least 18 years of age with histologically confirmed, relapsed, or refractory indolent and aggressive B-cell NHL were enrolled, provided they experienced disease progression after at least one prior therapy regimen, had a performance status of less than 2 according to the Eastern Cooperative Oncology Group criteria, were not pregnant or lactating, and had a life expectancy of more than 3 months. The patients were required to have CD20+ and CD22+ NHL, as determined by either immunohistochemistry or flow cytometry of tumor specimens obtained at any time before enrollment. The WHO classification of lymphoma subtypes was used for this report.[14,15] Within 4 weeks before receiving study treatment, patients were required to have a hemoglobin more than 8.0 g/dL, an absolute granulocyte count ≥ 1,500/μL, a platelet count ≥ 75,000/μL, a serum creatinine of ≤ 1.5× the upper limit of normal, a serum bilirubin ≤ 1.5× the upper limit of normal, absence of positive hepatitis B and C serology, and nonbulky disease ≤ 10 cm in the largest diameter. They were required to be at least 4 weeks beyond any chemotherapy, radiotherapy, or biologic therapy, and 2 weeks beyond corticosteroid use. All patients were rituximab naïve. Patients with CNS disease, HIV, or Richter's lymphoma were not eligible. The protocol was approved by the Weill Medical College of Cornell University–New York Presbyterian Hospital Institutional Review Board, and written informed consent was obtained from all patients.

Study End Points

Safety end points included the incidence of adverse events (AEs), including those occurring during or within 7 days of the MAb infusions and all later events deemed possibly or probably related to treatment, and change in the human antihuman antibody (HAHA) status, laboratory values, and infusion-day vital signs. AEs were recorded throughout the study and graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Monitoring included frequent hematology and serum chemistry profiles, periodic monitoring of immunoglobulins, and immunophenotyping of blood mononuclear cells. The patients were screened for serum anti-CD22 antibody (HAHA) using an enzyme-linked immunosorbent assay (Immunomedics Inc), which has a sensitivity of 5 ng/mL. Samples were obtained within 4 weeks before study entry, 24 hours after the last infusion, at restaging, and 3 months after the last treatment.

Efficacy

Responses were assessed according to the International Workshop NHL response criteria.[16] Bidimensional computed tomography data for the neck/chest and abdomen/pelvis were collected at screening, restaging, and follow-up visits for evaluation of disease response. Bone marrow aspirates and biopsies were performed at study entry and as required to confirm complete responses (CRs). Time to progression (TTP) was measured from first infusion until the first evidence of progression.

Statistical Analyses

All patients who received more than one dose of epratuzumab and rituximab were included in the safety and efficacy analyses. The analyses of the objective response (OR) rate for indolent and aggressive NHL and TTP were based on the assessable patient subset (all enrolled patients who received > one dose of epratuzumab and rituximab, and had ≥ one post-treatment

evaluation for response or had withdrawn from the study before the first post-treatment evaluation of response because of disease progression). Duration of response was analyzed for the patients who responded. Median duration of response and TTP were estimated using the Kaplan-Meier method.[17]

Patients

Between September 2000 and July 2002, 23 patients with indolent (n = 16) and aggressive (n = 7) NHL who received at least one dose of epratuzumab and rituximab were enrolled onto the study and included in the evaluation of safety. Twenty-two of these patients were included in the evaluation of efficacy; one patient withdrew consent after only one infusion of epratuzumab and rituximab because of pre-existing disease-related symptoms (pain), and was not included in the evaluation of efficacy because of inadequate post-treatment evaluation. Demographic and clinical characteristics for enrolled patients are listed in Table 1. Fifteen patients with follicular NHL, one patient with marginal-zone NHL, and seven patients with diffuse large B-cell lymphoma (DLBCL) were enrolled. Patients with indolent and

Table 1. Baseline Demographic and Clinical Characteristics for Patients Receiving at Least One Dose of Epratuzumab

Baseline Characteristic	Indolent Patients (n = 16)		Aggressive Patients (n = 7)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	64.5		67	
Range	31-84		26-86	
Females	10	63	4	57
No. of prior therapies				
Median	1		3	
Range	1-6		1-8	
Prior rituximab treatment	0		0	
Prior high-dose chemotherapy and stem-cell transplantation (%)	0		1	14
Response to last prior treatment	11	69	6	86
Time from end of last treatment, years				
Median	2.5		1	
Range	0.1-10.6		0-10.4	
Time from initial diagnosis, years				
Median	4.55		2.5	
Range	0.1-22.2		1-12.4	
WHO classification				
Diffuse, large B cell	—		7	100
Follicular grade I	4	25	—	
Follicular, grade II	11	69	—	
Marginal zone B-cell	1	6	—	
Stage of NHL: No. (%)				
III	8	50	4	57
IV	8	50	3	43
Bone marrow involvement	5	31	2	29
ECOG performance score = 0	4	25	1	14
Bulky disease at least 5 cm	9	56	3*	43
SPD, cm²				
Median	50.9*		22.1*	
Range	6.42-284		3.42-266	
LDH > normal	7	44	5	71
IPI				
1	3	19	1	14
2	9	56	1	14
3	4	25	4	57
4	—		1	14
Peripheral-blood B-cell counts, CD20				
Median	13		17	
Range	< 1-65		3-26	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SPD, sum of products of bidimensional measurements; LDH, lactate dehydrogenase; IPI, International Prognostic Index.
*Unknown for one patient.

aggressive NHL had similar demographic and clinical characteristics. Slightly more females than males were enrolled (63% with indolent and 57% with aggressive NHL, respectively). Additional characteristics included the following: 100% were stage III/IV and approximately one third had bone marrow involvement at study entry. Patients with indolent NHL had a median of 4.5 years from diagnosis, and patients with aggressive NHL had a median of 2.5 years from diagnosis. The median age was 64.5 years for indolent NHL patients (range, 31 to 84 years) and 67 years for DLBCL patients (range, 26 to 86 years). All patients had at least one prior therapy; there was a median of one prior therapy (range, one to six prior therapies) for indolent NHL patients and of three prior therapies (range, one to eight prior therapies) for aggressive NHL patients. No patient had received prior therapy with rituximab.

Safety

Treatment was well tolerated, and no dose-limiting toxicity was encountered. After seven patients received their week 1 doses separated by 2 days (treatment was received on days 1 and 3) without difficulty, subsequent patients received therapy with both epratuzumab and rituximab on days 1, 8, 15, and 22. Toxicities encountered during the course of treatment are summarized in Table 2. Most clinical AEs (91%) were mild to moderate (grade 1 or 2) and self-limited. The majority of patients experienced AEs during the first infusion, and both the incidence and frequency declined with subsequent infusions. Approximately 61% (14 patients) had AEs that were considered to be related (probably or possibly related, or of unknown relationship) to the study treatment. All AEs with at least a 10% frequency are reported in Table 2. Given the close temporal relationship of the administration of the agents, it is not possible to attribute AEs definitively to one antibody or the other. No clinically significant changes in laboratory measurements (including hematology values and serum chemistries or vital signs) were noted, and no serious

treatment-related AEs occurred. No patient developed HAHA against epratuzumab.

Rituximab in combination with epratuzumab ablated the blood B-cell levels for up to 6 months, as measured by $CD19^+$ and $CD20^+$ cell counts, but mean/median IgM, IgA, and IgG levels remained at baseline levels at all evaluations.

Responses to Treatment

In the 16 assessable patients with indolent NHL, the OR rate was 63% (10 of 16 patients), with nine patients (56%) achieving a CR or unconfirmed CR (CRu) and one patient achieving a partial response (PR), as listed in Figure 1. We also analyzed the CR rate of the indolent NHL population according to the follicular lymphoma international prognostic index score (FLIPI) at study entry.[6] The FLIPI is currently the most widely accepted prognostic assessment for indolent NHL. Of 16 indolent NHL patients, two of three patients with an intermediate-risk FLIPI score achieved a CR, whereas five of 13 patients (46%) with a high-risk FLIPI score achieved a CR or CRu. In the six assessable patients with DLBCL, the OR rate was 67% (four of six patients), with three CRs and one PR. An intent-to-treat analysis (including one patient who was considered inassessable because only one infusion was administered) results in an OR rate of 57% for the DLBCL group. The median time to response was 57 days. The median duration of remission for indolent and aggressive NHL has not been reached. Median TTP for indolent NHL was 17.8 months. The Kaplan-Meier curves of duration of remission and TTP are shown in Figures 2 and 3. Responses are ongoing in seven of the 16 patients with indolent NHL and three of the six patients with aggressive DLBCL.

Table 2. All Adverse Events With at Least 10% Incidence

Preferred Term	No. of Patients (n = 23)	%
Pyrexia	7	30
Rigors	7	30
Fatigue	5	22
Influenza-like illness	3	13
Pain NOS	3	13
Arthralgia	4	17
Pain in limb	3	13
Nausea	3	13
Headache NOS	4	17
Flushing	3	13

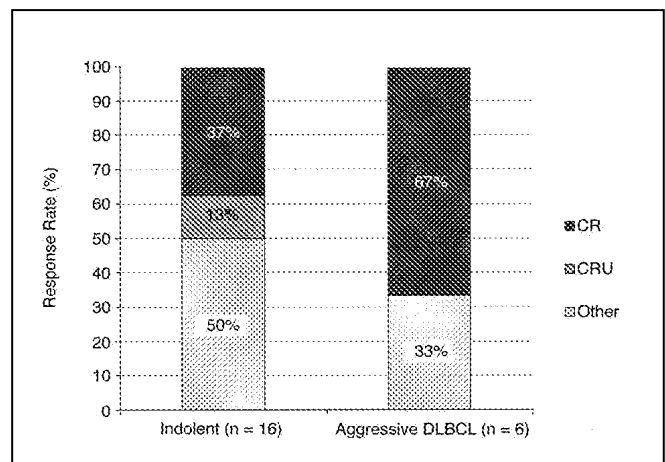Abbreviation: NOS, not otherwise specified.

Fig 1. Response rate for patients with indolent-follicular, indolent-other, and all indolent NHL, and aggressive diffuse large B-cell lymphoma. CR, complete response; CRU, unconfirmed CR.
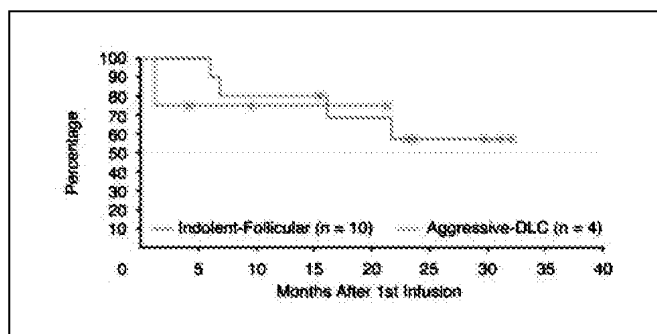
Fig 2. Kaplan-Meier curves of duration of response for patients with indolent-follicular and aggressive diffuse large B-cell lymphoma (DLBCL).

Therapy with rituximab is used widely in the treatment of indolent and aggressive NHL. In a registration trial that lead to initial approval, rituximab 375 mg/m² per week for 4 weeks in 166 patients with relapsed or refractory indolent NHL showed an OR rate of 48% (6% had CRs) and a median TTP of 13 months for responders.[10] In the follicular subset, response rates were higher (60%). In patients with aggressive NHL subtypes, rituximab therapy has an approximately 30% overall response rate, with a median of 8 months time to disease progression for responders.[18] AEs after single-agent rituximab treatment are generally brief and are usually related to the first infusion, but can include grade 3 and 4 toxicities.[10] With these encouraging results, the optimal use of rituximab in the treatment of indolent and aggressive NHL remains under active investigation, particularly through the use of maintenance therapy schedules.[19] Furthermore, there are continuing efforts to improve on the success of rituximab treatments for B-cell malignancies, including combinations with other biologic agents such as interleukin-2,[20,21] chemotherapy-rituximab
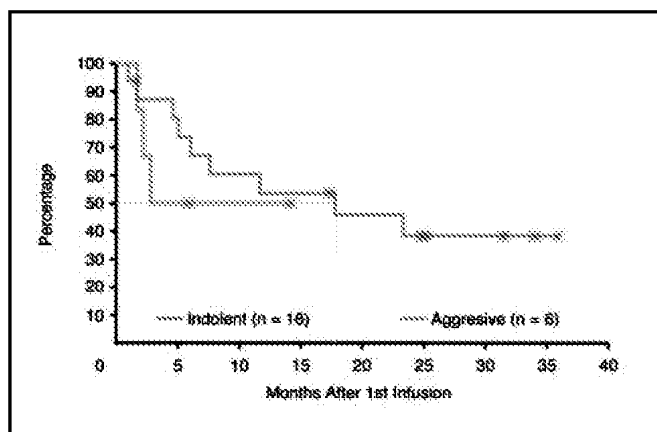

Fig 3. Kaplan-Meier curves of time to progression for all assessable patients (responders and nonresponders) with indolent and aggressive non-Hodgkin's lymphoma.

regimens (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab),[7,22-25] and the development of second-generation CD20 MAbs.[26-28] This report describes the first clinical trial to evaluate a combination antibody therapeutic regimen targeting two distinct B cell-specific targets (CD20 and CD22).

The hypothesis leading to this study was that antibodies directed against other B-cell antigens, and with potentially different mechanisms of action, might overcome any initial intrinsic resistance to rituximab, and could possibly also prove to be additive or synergistic when combined with rituximab. The candidate target chosen was CD22, a 135-kd transmembrane glycoprotein that is a B-lymphocyte–restricted member of the immunoglobulin superfamily, and a member of the sialoglycoprotein family of adhesion molecules that regulate B-cell activation and the interaction of B cells with T cells and antigen-presenting cells.[29,30] CD22 is detected on more than 85% of B-cell NHL.[13] Furthermore, preclinical data suggested that CD22 is an attractive target for B-cell–based therapy because of its restricted expression and potential enhancement of effects from an anti-CD20 therapy.[27]

The initial step in this approach included the development and characterization of a mouse monoclonal antibody (mLL2, formerly called EPB-2) that specifically binds to cluster C of human CD22.[31] Epratuzumab is a complementarity-determining region–grafted, humanized, IgG1 κ-engineered version of this murine MAb that is potentially more appropriate for repeated clinical use because less murine protein is present than in a chimeric MAb. Indeed, when naked and radiolabeled forms of epratuzumab were administered repeatedly to NHL patients, it was well tolerated and had virtually no immunogenicity.[12,13,32]

In vitro immunohistologic evaluations demonstrated an overlapping expression of CD20 and CD22 in samples of B-NHL.[33,34] Mechanistically, epratuzumab has not been found to cause B-cell killing by apoptosis or complement-mediated cytotoxicity, but has shown modest antibody-dependent cellular cytotoxicity when tested on NHL cell lines.[35] In contrast, all three mechanisms of action have been reported for rituximab,[36] as well as for other recently developed human CD20 MAb.[26,27] The mechanism of action of epratuzumab may in part be related to its rapid internalization after its binding to CD22-expressing lymphoma cells.[37]

We demonstrated single-agent activity of epratuzumab in phase I/II, single-center, open-label, dose-escalation studies in patients with NHL who had experienced disease relapse after conventional chemotherapy or rituximab treatment. In these studies, 55 patients with indolent NHL and 56 patients with aggressive NHL received once-weekly epratuzumab 120, 240, 360, 480, 600, and 1,000 mg/m² administered for 4 consecutive weeks.[12,13] In addition, 11 patients tolerated two treatment cycles, whereas one patient

underwent three treatment courses.[38] Dose-limiting toxicity was not encountered in the initial dose escalation, and the study was expanded following additional experience at intermediate dose levels to include more patients receiving the 360 mg/m^2/wk dosing in the phase II arm. At this dose, six of 14 patients (43%) with follicular NHL and two of 13 patients (15%) with DLBCL achieved an objective response,[12,13] and several CRs were noted. Given that both anti-CD22 and anti-CD20 have clinical activity, through binding to different targets, evaluation of a combination regimen is clearly of interest.

In vitro studies also supported the potential improved efficacy of this antibody combination because of the observation that rituximab therapy could upregulate the expression of CD22.[33,35] Furthermore, murine experiments with human NHL xenografts showed that epratuzumab in combination with rituximab or with another CD20 MAb, hA20, may be more efficacious than either monotherapy.[27] We speculate that rapid internalization of CD22, especially after binding with epratuzumab, may result in activation of nonreceptor tyrosine kinases associated with phosphorylation of the cytoplasmic tail of CD22, as well as negative regulation of the B-cell antigen receptor, which could increase the antilymphoma effects of anti-CD20 agents.[33,35]

In this pilot trial, toxicity to the combination antibody regimen was similar in nature and degree to that previously reported with rituximab monotherapy. Though this is a small study, the OR rates were 63% and 67% with this outpatient, four-dose course of therapy of rituximab in combination with epratuzumab for patients with relapsed indolent and aggressive (DLBCL) NHL, respectively. It is important to note, however, that most (13 of 16) of the indolent NHL patients had a high-risk FLIPI score at study entry, although they also demonstrated some favorable prognostic features (median, one prior treatment regimen; median, 2.5 years since last therapy; rituximab naive). The aggressive NHL patients were more heavily pretreated (median, three prior treatment regimens), although their outcomes with the immediate prior therapy suggest that they may be characterized as more commonly having relapsed rather than refractory disease. With these caveats, the high CR rate in patients with recurrent NHL is noteworthy. Most of the responses were CR/CRu (56% for indolent/follicular NHL and 42% for DLBCL), which is uncommon for a well-tolerated biologic agent regimen in the setting of relapsed lymphoma.

Although patient characteristics differ across studies, it is encouraging that these CR rates are higher than the CR rate reported previously for rituximab alone in comparable dosing schedules.[10] Although one should be cautious in making any comparisons, Witzig et al[16] treated a cohort of 70 patients (83% with recurrent follicular lymphoma) using single-agent rituximab 375 mg/m^2 weekly for 4 weeks) in a study that also prospectively used the current International Workshop NHL response criteria. These investigators reported a CR rate of 16% and a CRu rate of 4%.[39] Preliminary results of two follow-up multicenter studies of epratuzumab plus rituximab also support the idea that some patients with B-cell NHL may demonstrate improved outcomes with a combination antibody approach.[40,41]

Although followup and further analysis are ongoing, initial results from these studies suggest that subsets of patients (including small lymphocytic lymphoma, DLBCL, and some follicular types) might benefit from the addition of epratuzumab to rituximab. However definitive conclusions cannot yet be made given the heterogeneous patient populations (histologies and prior therapies), short followup, limited subgroup numbers, and lack of a control (single antibody) comparison group. One could also speculate that there may be tumor types, based on antigen expression patterns, that could particularly benefit from combination antibody therapy. These groups might be identified through larger followup studies. Other approaches have been evaluated for their potential to augment the activity of rituximab. These include the addition of chemotherapy, the coadministration of immunostimulatory or proapoptotic agents, and the incorporation of a radioactive isotope.[21,23,42-44] Although efficacy data have shown benefits in some cases, these approaches may be limited by toxicities (including cytopenias, constitutional symptoms) and patient selection restrictions (eg, degree of bone marrow involvement).[40,44] The incorporation of a second active antibody without clinically meaningful additional toxicity, as in this report, is a particularly attractive strategy from the standpoint of limiting toxicity to patients.

The high CR rate and excellent tolerability of the combination of the CD20 and CD22 antibodies used in this study suggest a number of new possibilities for the treatment of indolent (follicular) NHL; this combination therapy should be tested in a large randomized study of patients with recurrent/refractory indolent NHL (to compare single-agent with combination therapy). The encouraging initial results observed for the combination in a small number of patients with DLBCL also suggest that this should be expanded in a cohort of patients with this aggressive form of NHL. If confirmed, this well-tolerated combination therapy may represent an acceptable alternative for patients with DLBCL who may have difficulty tolerating intensive chemotherapy, or in those who either may not be candidates for high-dose chemotherapy with peripheral stem-cell support or have experienced disease relapse after it.[43] A pilot study of cyclophosphamide, doxorubicin, vincristine, and prednisone plus epratuzumab and rituximab in first-line therapy for DLBCL has shown promising results,[45] and a larger multicenter study is under development.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors have completed the disclosure declaration, the following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Dave SS, Wright G, Tan B, et al: Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 351:2159-2169, 2004

2. Hans CP, Weisenburger DD, Greiner TC, et al: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275-282, 2004

3. Rosenwald A, Wright G, Chan WC, et al: The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346:1937-1947, 2002

4. Siebert R, Rosenwald A, Staudt LM, et al: Molecular features of B-cell lymphoma. Curr Opin Oncol 13:316-324, 2001

5. Marcus R, Imrie K, Belch A, et al: CVP chemotherapy plus Rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105:1417-1423, 2005

6. Solal-Celigny P, Roy P, Colombat P, et al: Follicular lymphoma international prognostic index. Blood 104:1258-1265, 2004

7. Coiffier B, Salles G: Immunochemotherapy is the standard of care in elderly patients with diffuse large B-cell lymphoma. Blood 104:1584-1585, 2004

8. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

9. Fisher RI, Shah P: Current trends in large cell lymphoma. Leukemia 17:1948-1960, 2003

10. McLaughlin P, Grillo-Lopez AJ, Link BK, et al: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. J Clin Oncol 16:2825-2833, 1998

11. Dorken B, Moldenhauer G, Pezzutto A, et al: HD39 (B3), a B lineage-restricted antigen whose cell surface expression is limited to resting and activated human B lymphocytes. J Immunol 136:4470-4479, 1986

12. Leonard JP, Coleman M, Ketas JC, et al: Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma. J Clin Oncol 21:3051-3059, 2003

13. Leonard JP, Coleman M, Ketas JC, et al: Epratuzumab, a humanized anti-CD22 antibody, in aggressive non-Hodgkin's lymphoma: Phase I/II clinical trial results. Clin Cancer Res 10:5327-5334, 2004

14. Harris NL, Jaffe ES, Diebold J, et al: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 17:3835-3849, 1990

15. Jaffe ES, Harris NL, Diebold J, et al: World Health Organization Classification of lymphomas: A work in progress. Ann Oncol 9:S25-S30, 1998 (suppl 5)

16. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 17:1244-1253, 1999

17. Kaplan EL: Nonparametric estimation for incomplete observations. J Am Stat Assoc 53:457-481, 1958

18. Coiffier B, Haioun C, Ketterer N, et al: Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. Blood 92:1927-1932, 1998

19. Hainsworth JD: Prolonging remission with rituximab maintenance therapy. Semin Oncol 31:17-21, 2004

20. Eisenbeis CF, Grainger A, Fischer B, et al: Combination immunotherapy of B-cell non-Hodgkin's lymphoma with rituximab and interleukin-2: A preclinical and phase I study. Clin Cancer Res 10:6101-6110, 2004

21. Gluck WL, Hurst D, Yuen A, et al: Phase I studies of interleukin (IL)-2 and rituximab in B-cell non-Hodgkin's lymphoma: IL-2 mediated natural killer cell expansion correlations with clinical response. Clin Cancer Res 10:2253-2264, 2004

22. Cheson BD: CHOP plus rituximab: Balancing facts and opinion. N Engl J Med 346:280-282, 2002

23. Czuczman MS: CHOP plus rituximab chemoimmunotherapy of indolent B-cell lymphoma. Semin Oncol 26:88-96, 1999

24. Czuczman MS, Fallon A, Mohr A, et al: Rituximab in combination with CHOP or fludarabine in low-grade lymphoma. Semin Oncol 29:36-40, 2002

25. Czuczman MS, Weaver R, Alkuzweny B, et al: Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 22:4711-4716, 2004

26. Teeling JL, French RR, Cragg MS, et al: Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. Blood 104:1793-1800, 2004

27. Stein R, Qu Z, Chen S, et al: Characterization of a new humanized anti-CD20 monoclonal antibody, IMMU-106, and its use in combination with the humanized anti-CD22 antibody, epratuzumab, for the therapy of non-Hodgkin's lymphoma. Clin Cancer Res 10:2868-2878, 2004

28. Nagajothi N, Matsui WH, Mukhina GL, et al: Enhanced cytotoxicity of rituximab following genetic and biochemical disruption of glycosylphosphatidylinositol anchored proteins. Leuk Lymphoma 45:795-799, 2004

29. Engel P, Nojima Y, Rothstein D, et al: The same epitope on CD22 of B lymphocytes mediates the adhesion of erythrocytes, T and B lymphocytes, neutrophils, and monocytes. J Immunol 150:4719-4732, 1993

30. Engel P. CD22. J Biol Regul Homeost Agents 14:295-298, 2000

31. Stein R, Belisle E, Hansen HJ, et al: Epitope specificity of the anti-(B cell lymphoma) monoclonal antibody, LL2. Cancer Immunol Immunother 37:293-298, 1993

32. Sharkey RM, Brenner A, Burton J, et al: Radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-DOTA humanized anti-CD22 IgG (^{90}Y-Epratuzumab): Do tumor targeting and dosimetry predict therapeutic response? J Nucl Med 44:2000-2018, 2003

33. Cesano A, Gayko U: CD22 as a target of passive immunotherapy. Semin Oncol 30:253-257, 2003

34. Siegel AB, Goldenberg DM, Cesano A, et al: CD22-directed monoclonal antibody therapy for lymphoma. Semin Oncol 30:457-464, 2003

35. Carnahan J, Wang P, Kendall R, et al: Epratuzumab, a humanized monoclonal antibody targeting CD22: Characterization of in vitro properties. Clin Cancer Res 9:3982S-3990S, 2003

36. Maloney DG, Smith B, Rose A: Rituximab: Mechanism of action and resistance. Semin Oncol 29:2-9, 2002

37. Shih LB, Lu HH, Xuan H, et al: Internalization and intracellular processing of an anti-B-cell lymphoma monoclonal antibody, LL2. Int J Cancer 56:538-545, 1994

38. Furman RR, Coleman M, Leonard JP: Epratuzumab in non-Hodgkin's lymphomas. Curr Treat Options Oncol 5:283-288, 2004

39. Witzig TE, Gordon LI, Cabanillas F, et al: Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 20:2453-2463, 2002

40. Strauss SJ, Lister TA, Morschauser F, et al: Multi-center, phase II study of combination antibody therapy with epratuzumab plus rituximab in relapsed/refractory indolent and aggressive NHL: Promising preliminary results. J Clin Oncol 23:577, 2004 (suppl; abstr 6579)

41. Emmanouilides C, Leonard JP, Schuster SJ, et al: Multi-center, phase 2 study of combination antibody therapy with epratuzumab plus rituximab in recurring low-grade NHL. Blood 102:69a, 2003

42. Witzig TE, White CA, Gordon LI, et al: Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. J Clin Oncol 21:1263-1270, 2003

43. Coiffier B: New treatment strategies in lymphomas: Aggressive lymphomas. Ann Hematol 83:S73-S74, 2004 (suppl 1)

44. Leonard JP, Coleman M, Hainsworth JD, et al: Phase II study of oblimersen sodium (G3139) alone and with R-CHOP in mantle cell lymphoma (MCL). Proc Am Soc Clin Oncol 22:566, 2003 (abstr 2276)

45. Micallef IN, Kahl BS, Gayko U, et al: Initial results of a pilot study of epratuzumab and rituximab in combination with CHOP chemotherapy (ER-CHOP) in previously untreated patients with diffuse large B-cell lymphoma (DLBCL). J Clin Oncol 23:577, 2004 (suppl; abstr 6580)